Connectivity Abnormalities in Psychiatric Disorders

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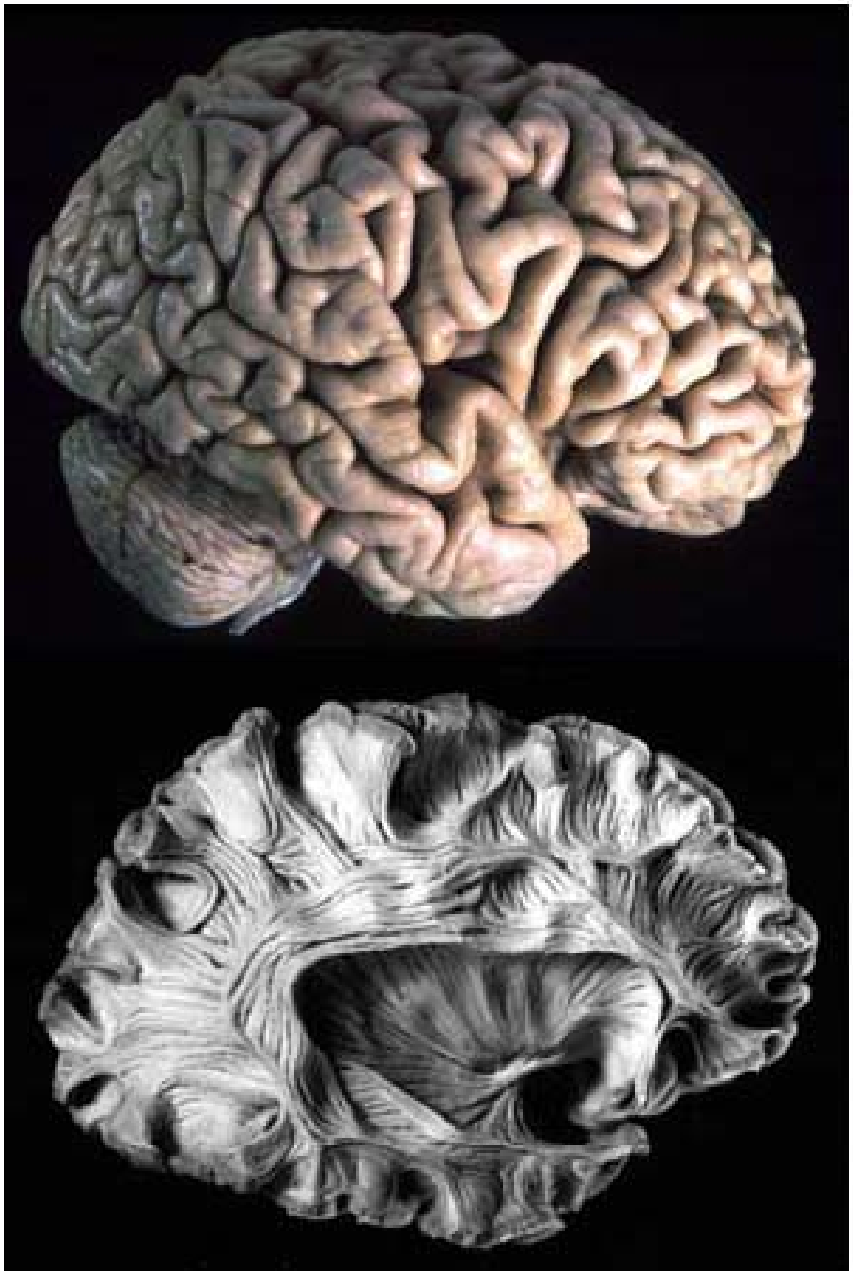
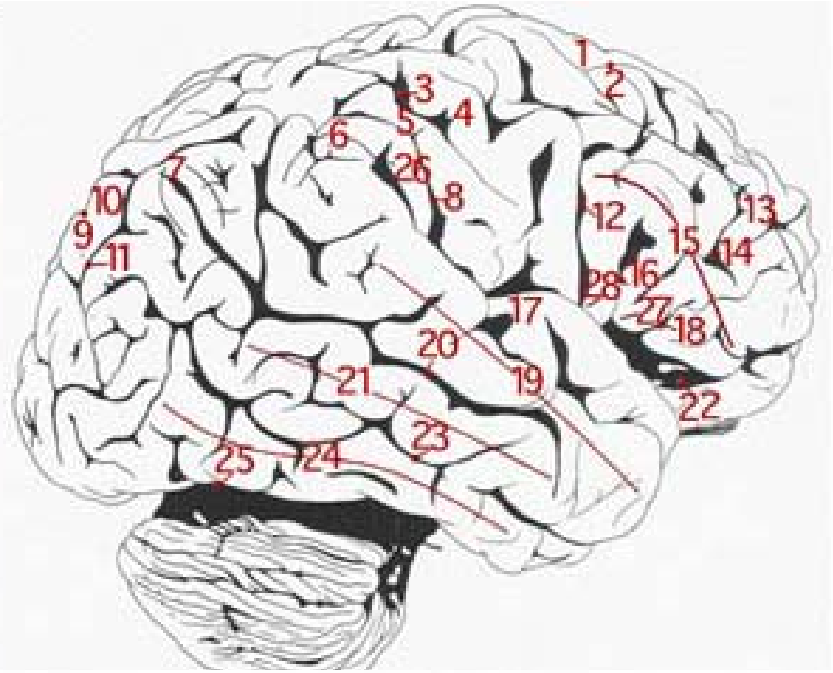
Disclosures

- Declaration of Financial Interests & Conflicts: None
- I will discuss the investigational use of the following in my presentation: None

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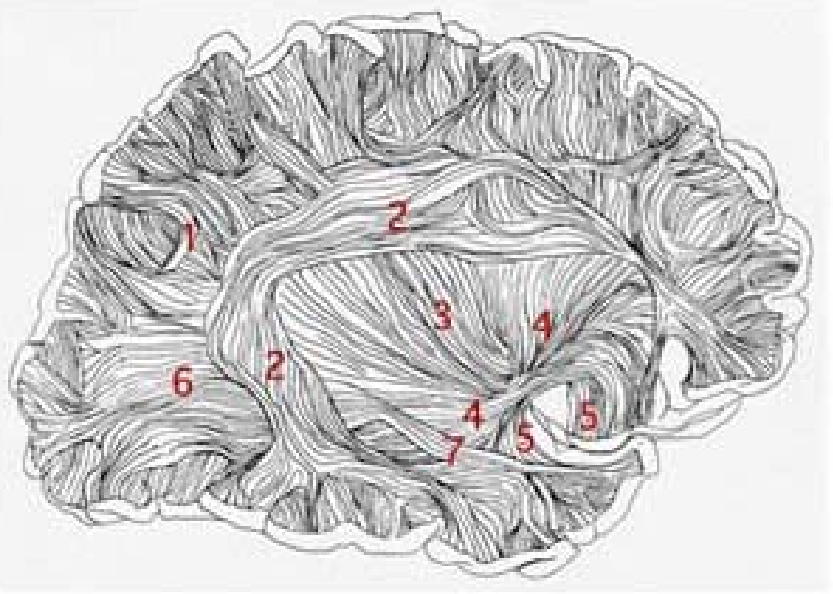
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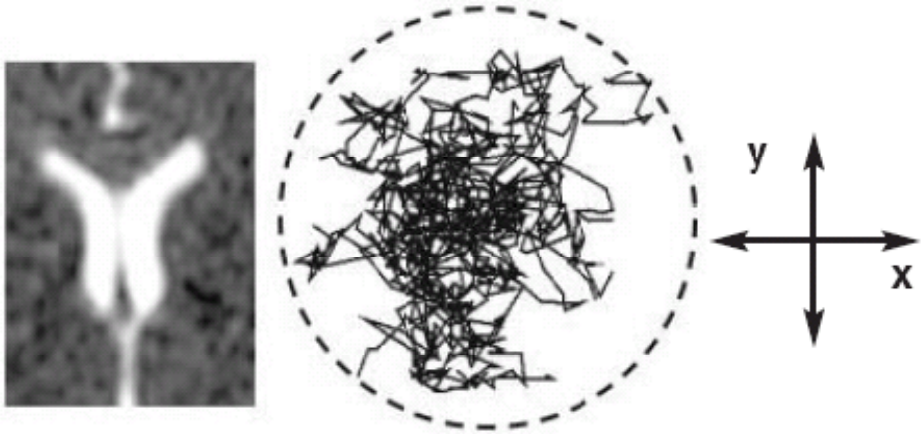
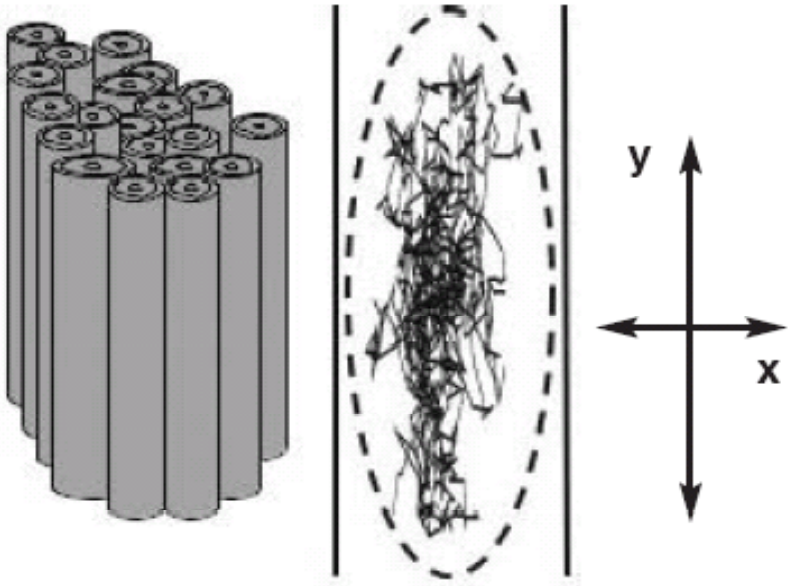
Outline

- Multimodal Connectivity Imaging
  - DTI/DSI - Anatomical –wiring defect
  - Resting fMRI - Functional – signaling defect
- Network Analysis Approaches
  - Graph Theory
  - Multivariate
  - Graph metrics based on correlation strength
  - Network based statistics

Water self diffusion



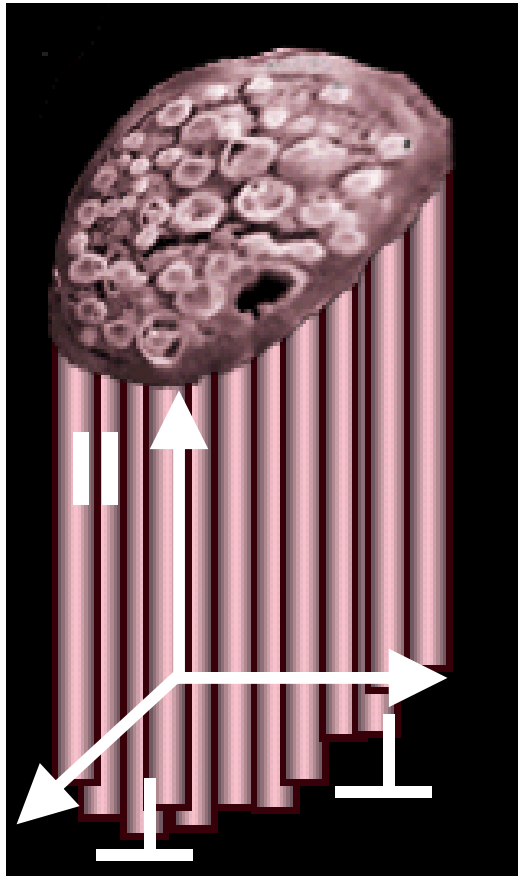
Isotropic
Diffusion



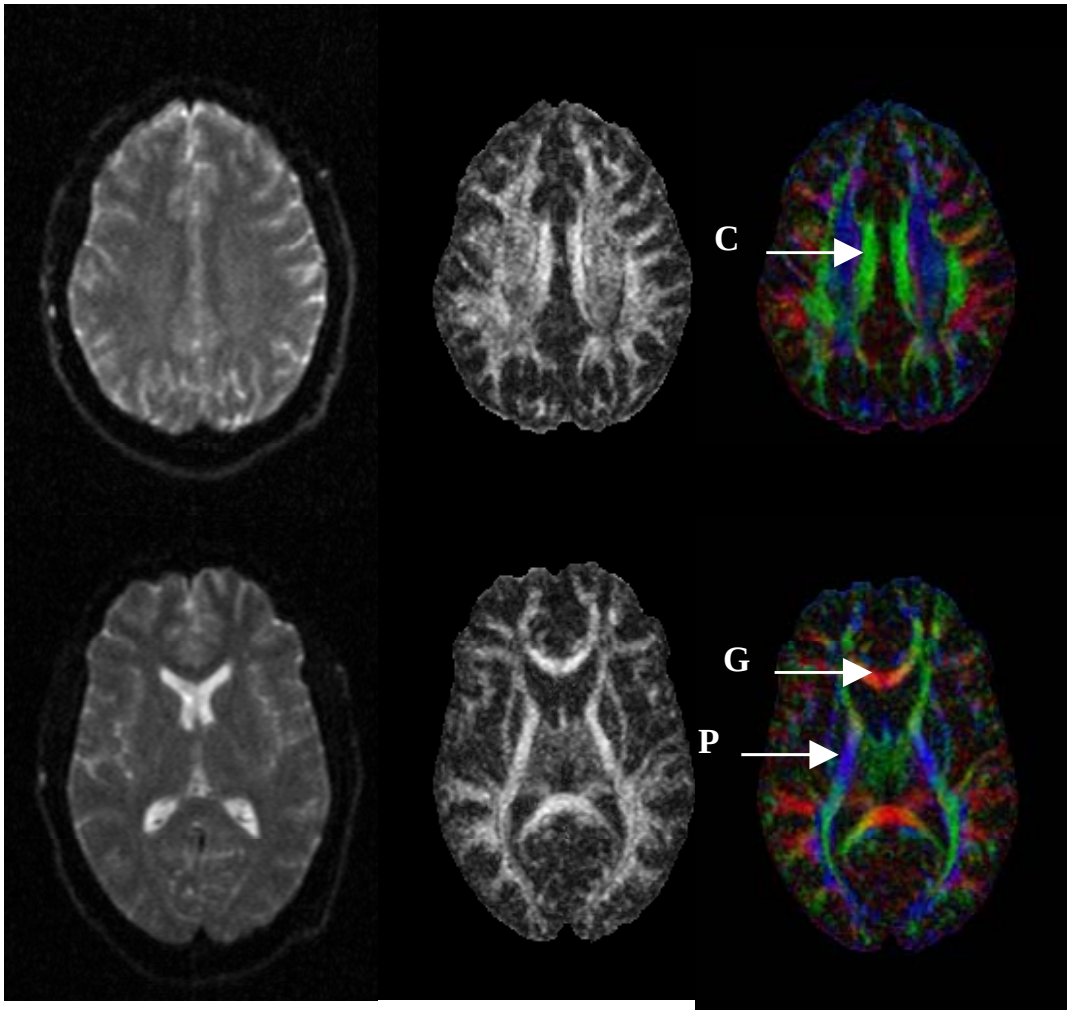
Anisotropic
Diffusion

DIFFUSION TENSOR-metrics

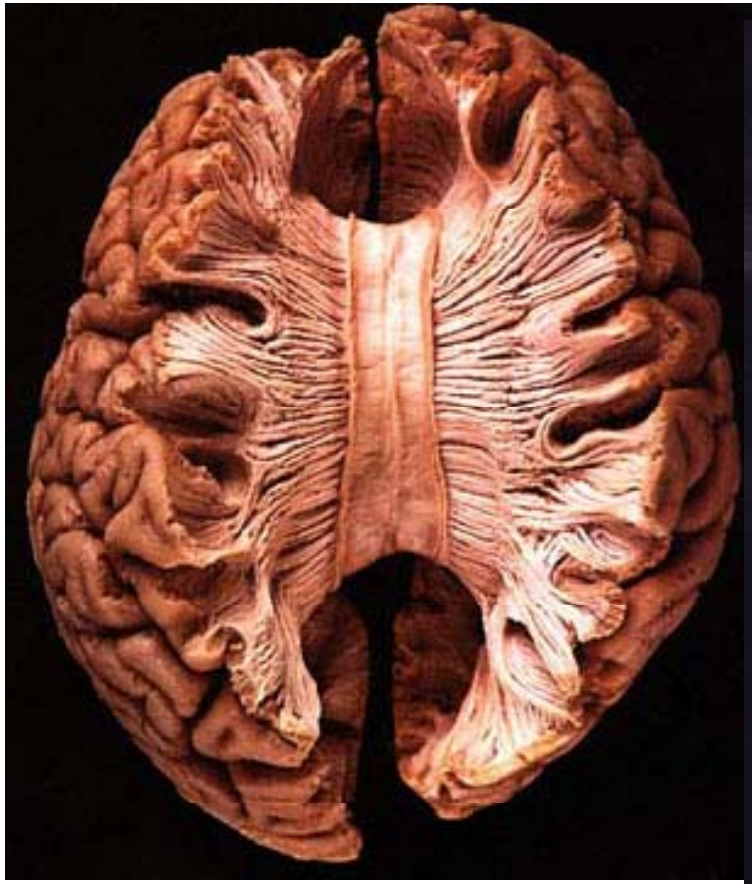
- SCALAR - magnitude
  - Diffusivity
    - trace - average diffusivity
    - Radial, axial
  - Anisotropy
    - Fractional, relative, lattice
- VECTOR - magnitude and direction
  - show predominant direction and magnitude of the diffusion

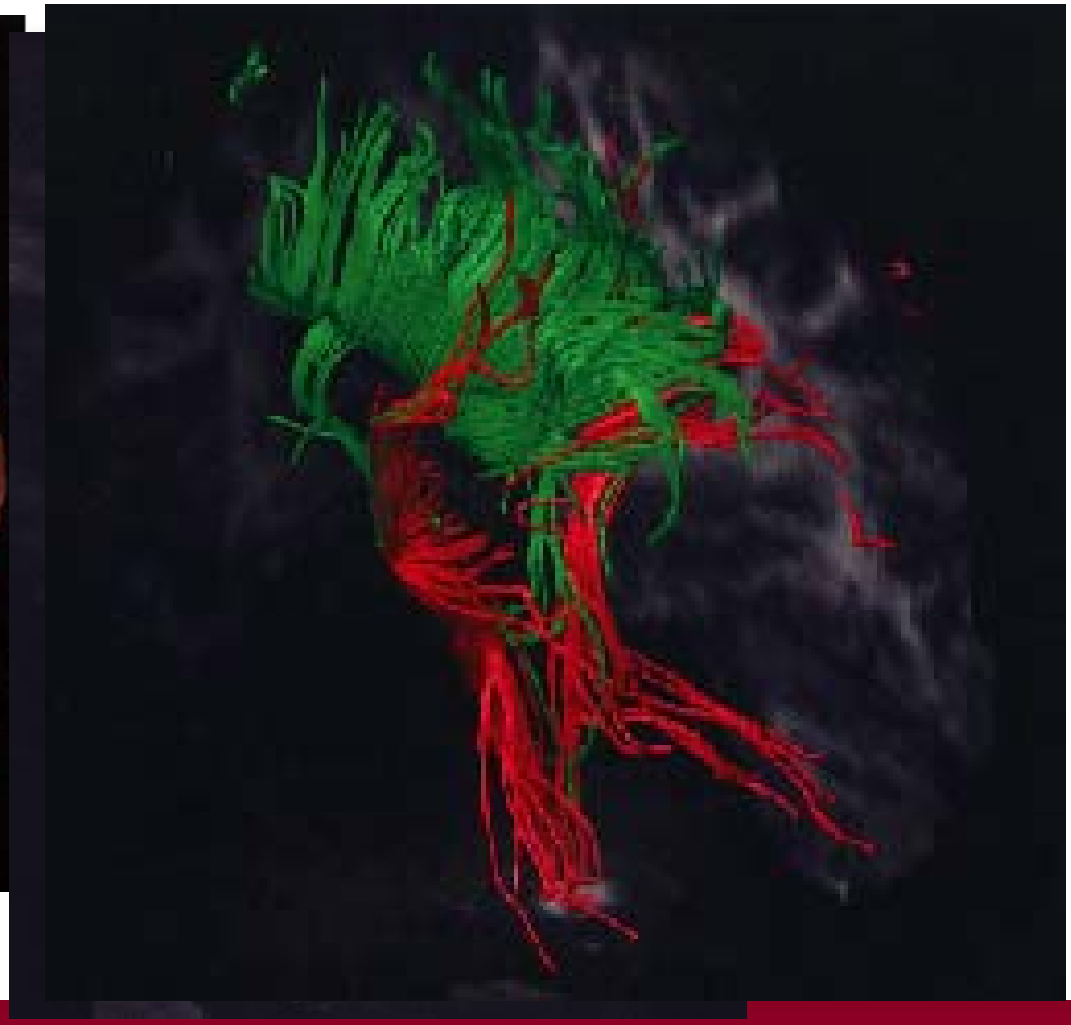


DTI Reveals White Matter Structure



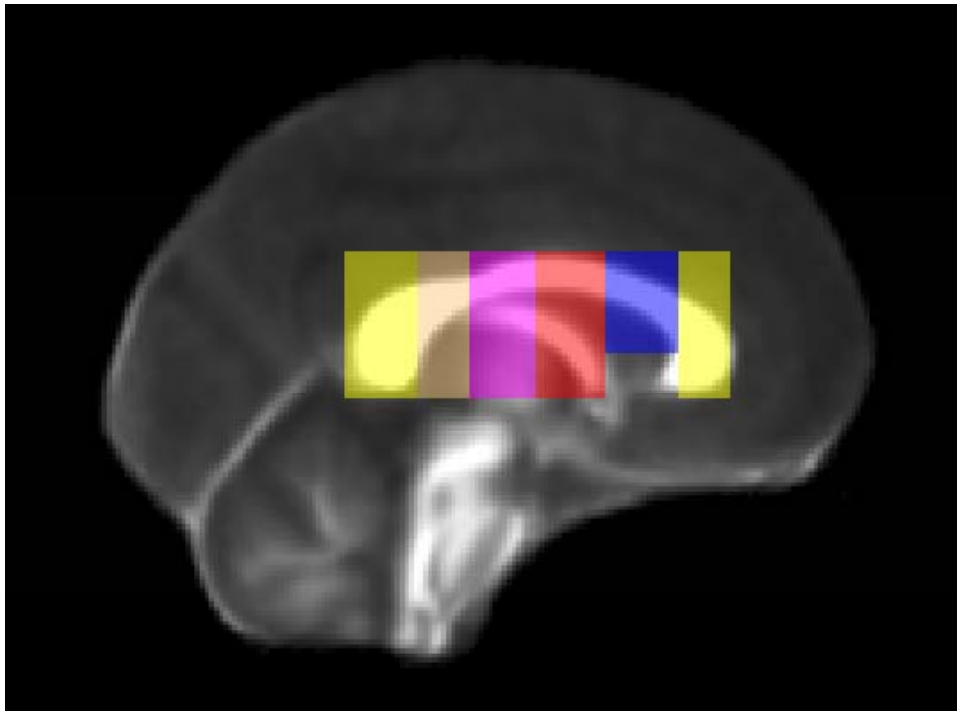
Tractography: Corpus Callosum

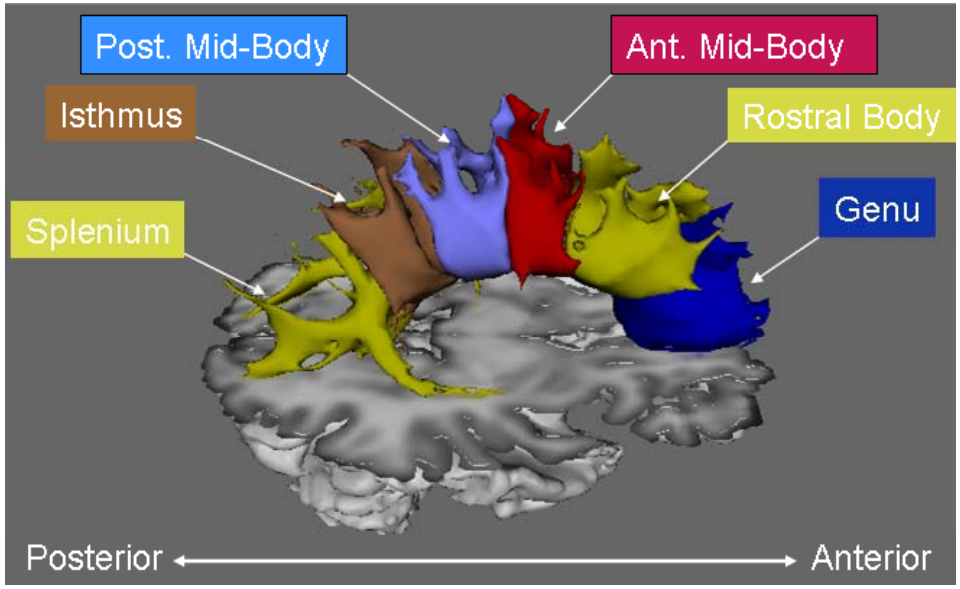




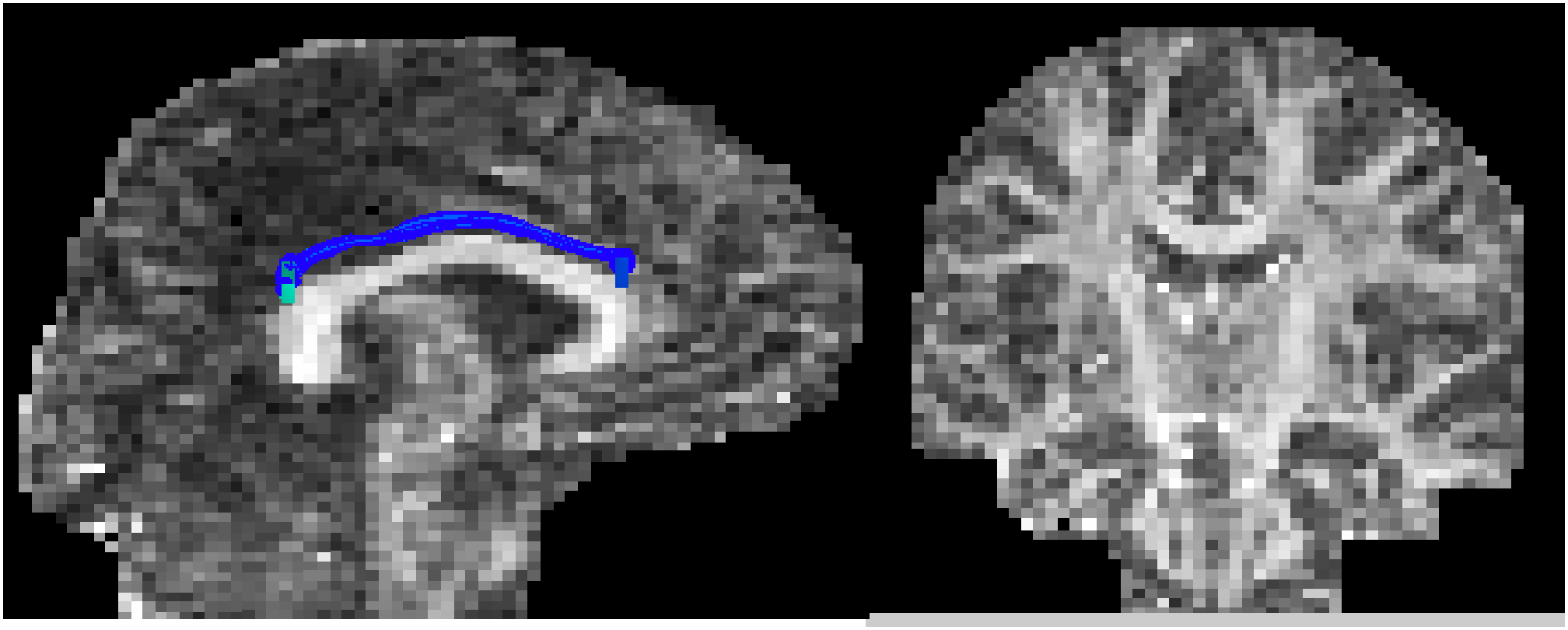
Jones et al. HBM 2002

Interhemispheric Tracts

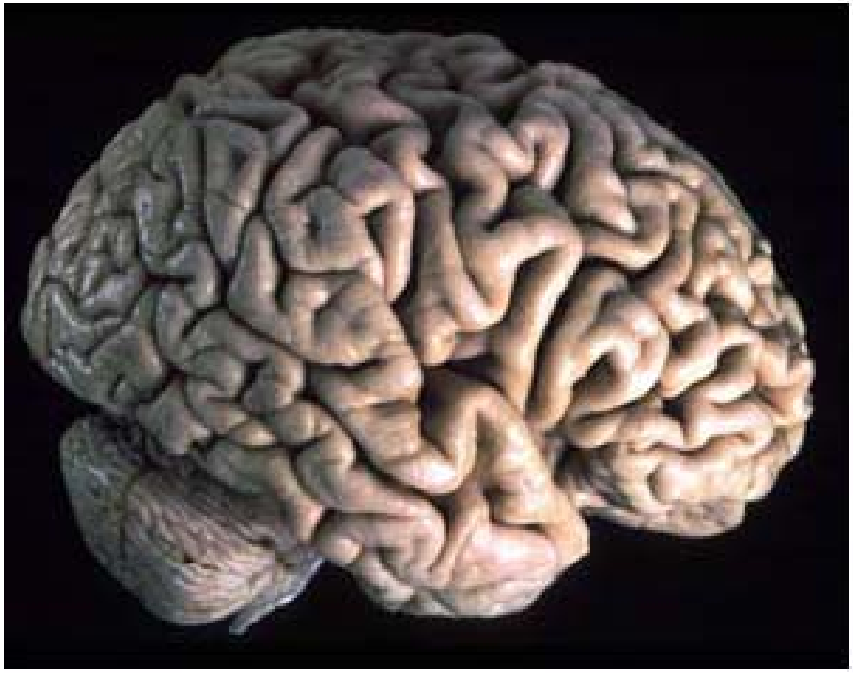


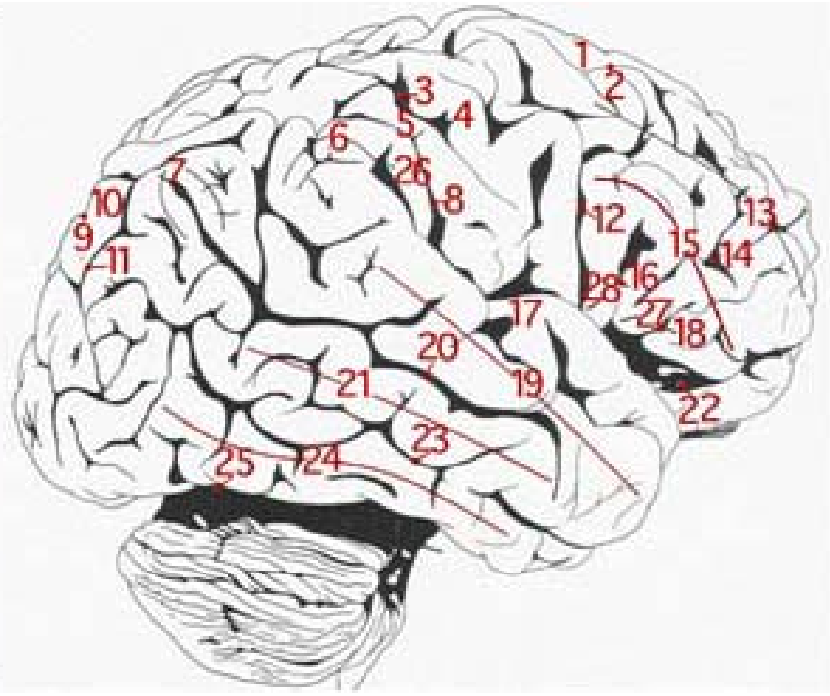


Caveat: Source Data Resolution!



Functional Brain Connectivity





Brain Activity

- Activity
  - Evoked activity - use of a task
  - Intrinsic activity - no task, resting state
- Metabolism
  - 80% of brain energy budget devoted to maintaining connections (Raichle and Mintun, Ann Rev Neurosci, 2006)
  - Adding evoked activity increases energy consumption by 1%
  - Suggests importance of intrinsic activity

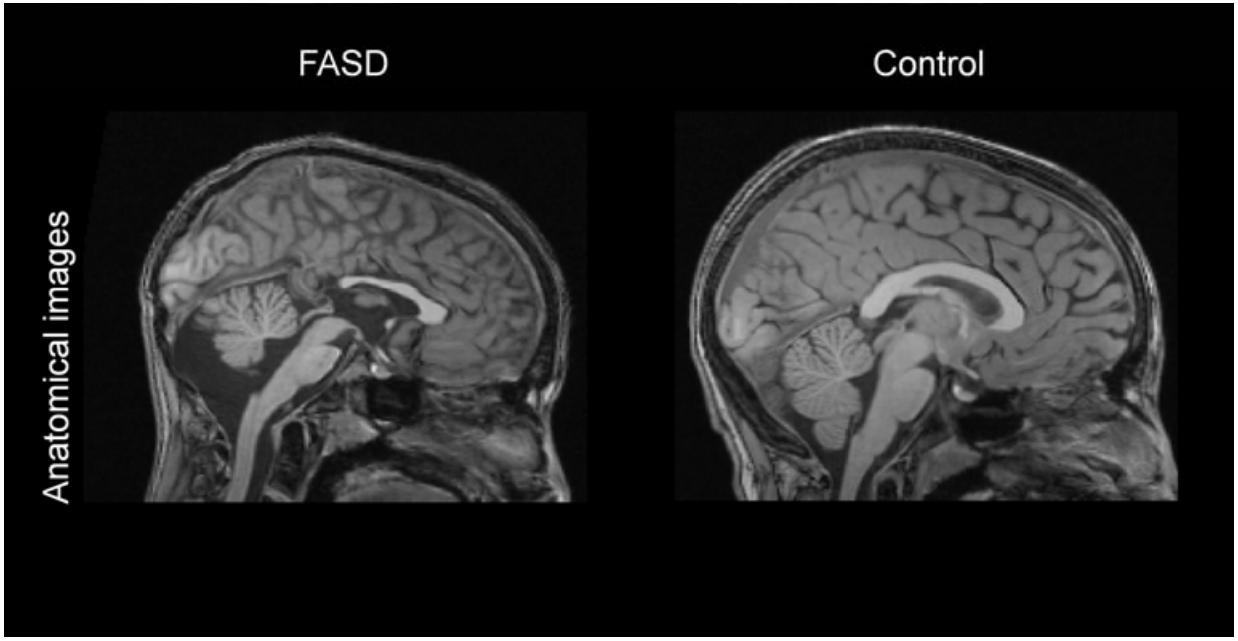
Fetal Alcohol Spectrum Disorders (FASD) represent a serious public health problem

- In the US 13% knowingly drink while pregnant
- 1% drink heavily while pregnant
- 3-4% binge drink during pregnancy (SAMHSA)
- 12% of pregnant women consume 5 or more drinks per month
- 50% of pregnancies are unplanned
- Fetal Alcohol Syndrome: 1 per 1000 live births
- Fetal Alcohol Spectrum Disorder (includes all conditions) is estimated to be 1 per 100

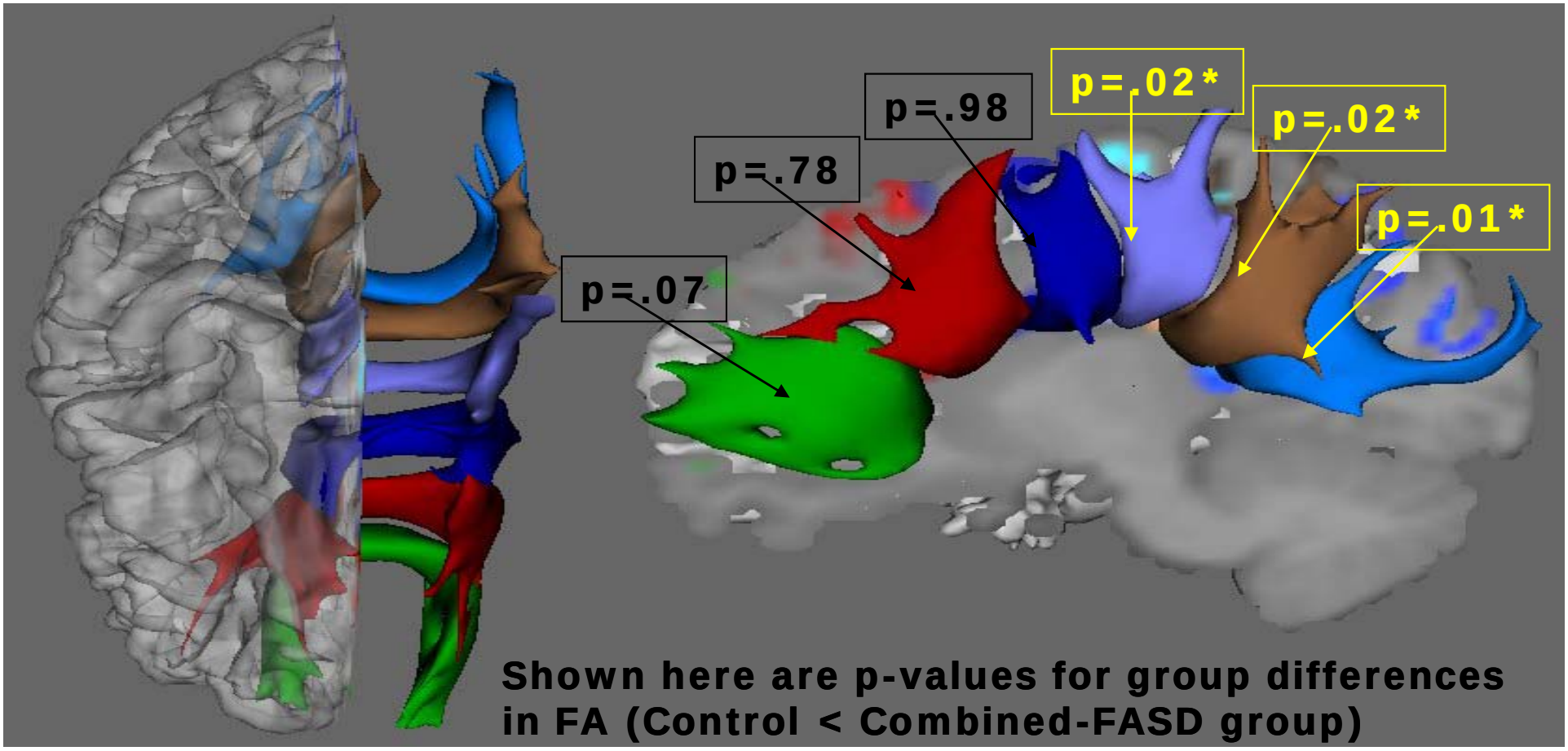
- Minnesota has the 7th highest rate of heavy drinking women of child bearing age

CDC. Morbidity and Mortality Weekly Reports, 51(13)

Sokol, R.J. et al. 2003, JAMA, 290(22)


FASD
Control
Anatomical images

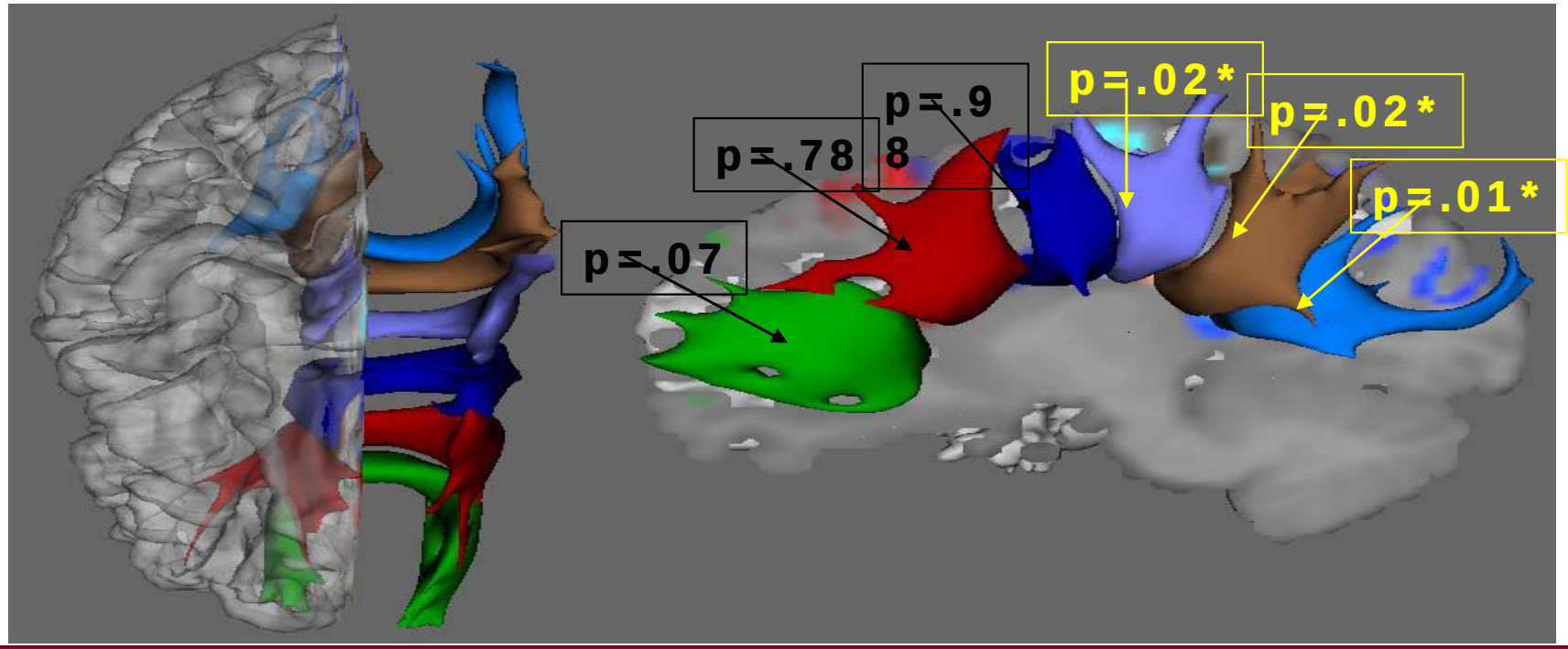
Corpus callosum abnormalities using probabilistic tractography (Wozniak et al, 2009)



Interhemispheric rsfMRI abnormalities

Anterior CC Connectivity: F = .7, p = .40, NS
Middle CC Connectivity: F = 1.36, p = .25, NS
Posterior CC Connectivity: F = 4.75, p = .03, effect size = .73

Posterior CC Connectivity correlates only with isthmus MD (r=-.42, p = .004)

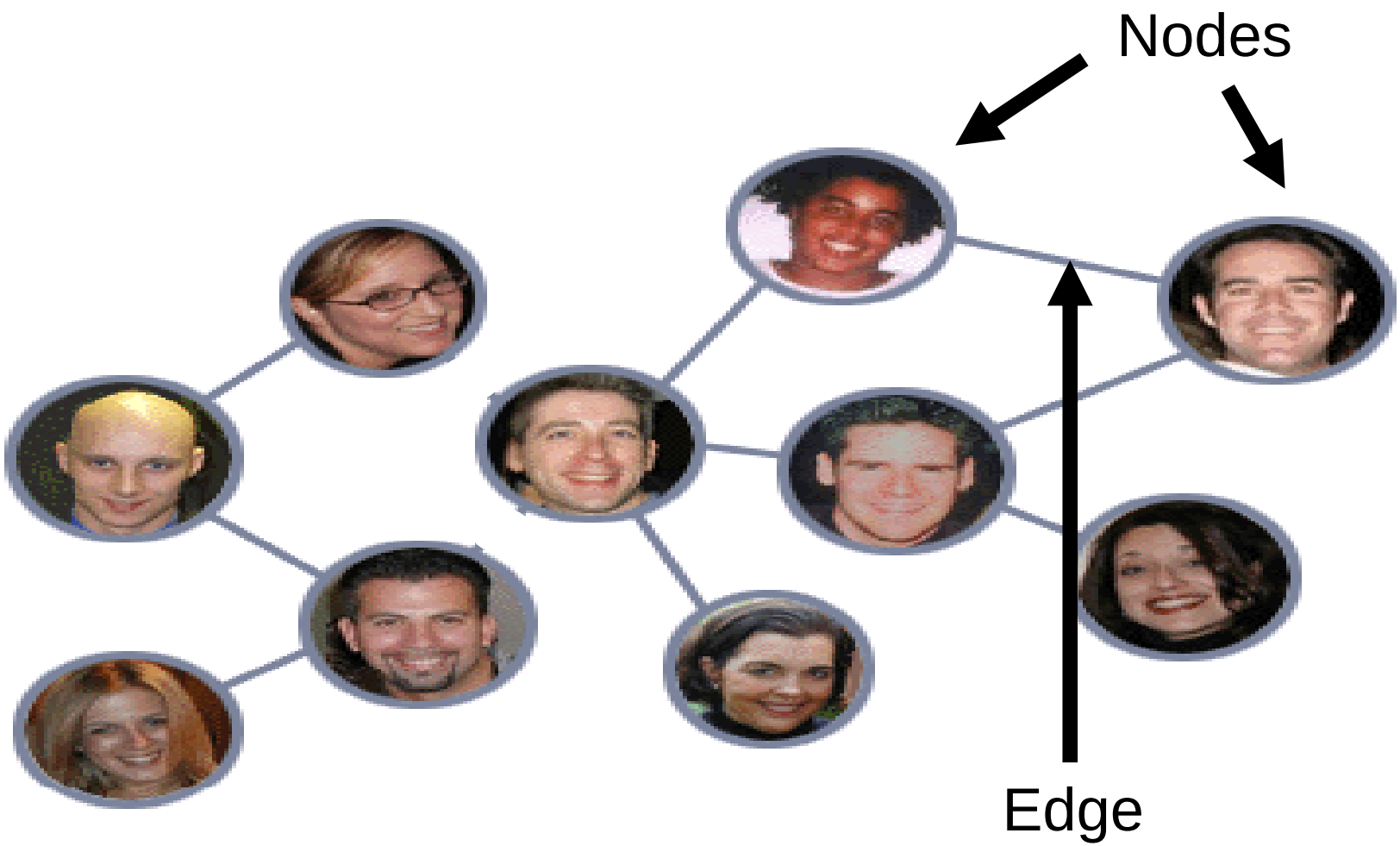


How to go beyond point to point analysis?

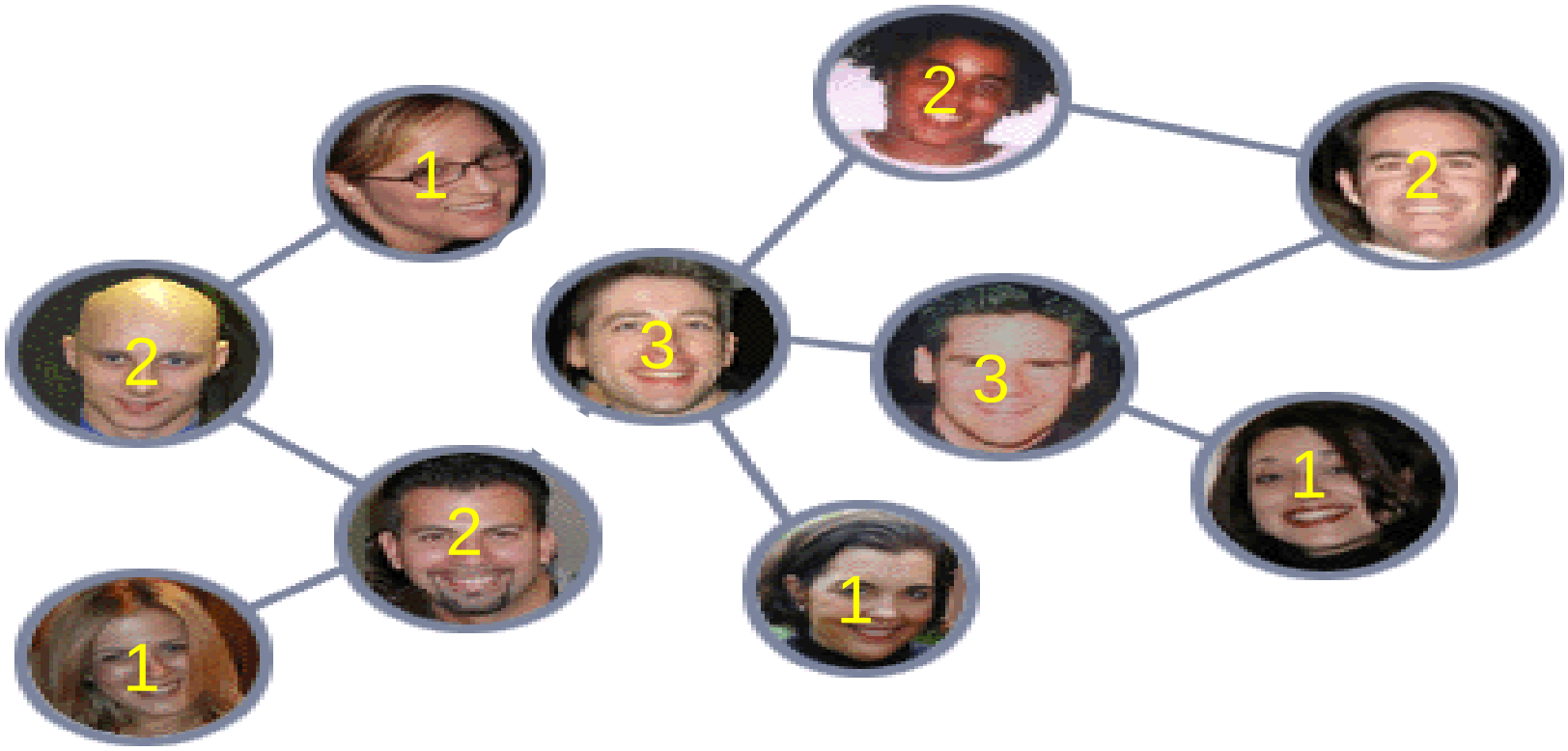
Graph Theory

- Branch of mathematics that provides mathematical framework for analyzing a network
- Quantitative Topographical Measures
  - Clustering coefficient – connection density
  - Path length – wiring efficiency
  - Global efficiency – parallel processing
  - Local efficiency – fault tolerance

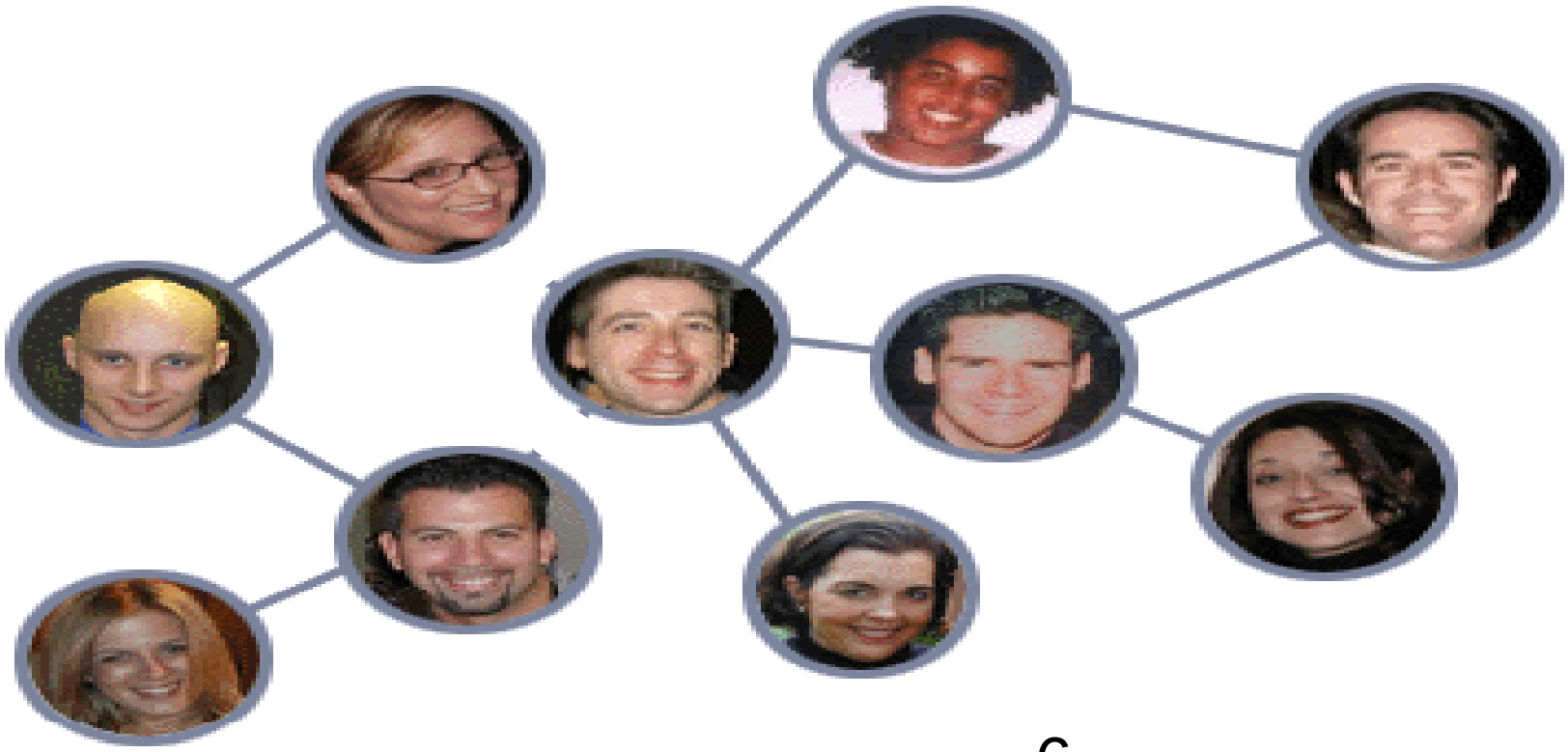
Social Network



Degree



Largest Connected Component



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Networks

TYPE	NODES	EDGES
Social	People	Friendships
Functional Brain network	Anatomical regions	Correlation of activity
Anatomical Brain network	Anatomical regions	Number of tractography streamlines

Subjects and Scanning

- 29 chronic schizophrenia patients (11 females, age: M = 41.3, SD = 9.3)
- 29 healthy participants (11 females, age M = 41.1, SD = 10.6)
- Siemens Trio 3T scanner
- T1 MPRAGE volumetric 1mm^3
- Resting state fMRI scan (eyes closed, awake) 6 min, TR=2sec, TE=30ms, FA=90 deg, 34 contig AC-PC aligned slices, 3.4x3.4x4mm^3
- Fieldmap (TR=300ms,TE=1.91/4.37ms, FA=55deg, 34 slices, 3.4x3.4x4.0 mm^3)
- DTI data - 30 directions, 2x2x2 mm^3

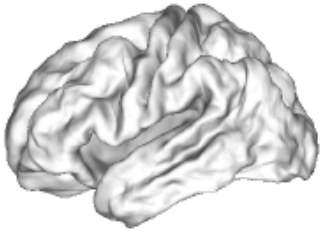
Connectivity Matrices

- FMRI
  - Standard FMRI preprocessing
  - Average timecourses were extracted from 90 anatomical regions of interest (nodes) defined by the AAL atlas
  - Movement regressed
  - Wavelet transform was computed for each timecourse
  - For the frequency range .06-.125Hz, a 90x90 correlation matrix was created.
- DTI
  - Standard DTI preprocessing
  - Streamline were calculation with a FACT-based algorithm from TrackVis Diffusion Toolkit (trackvis.org)
  - Custom software was written to calculate the number of streamlines connecting each of the 90 AAL nodes
  - Nodal degree (number of connections that link a node to another) was computed to create a 90x90 matrix

Multivariate Complexity

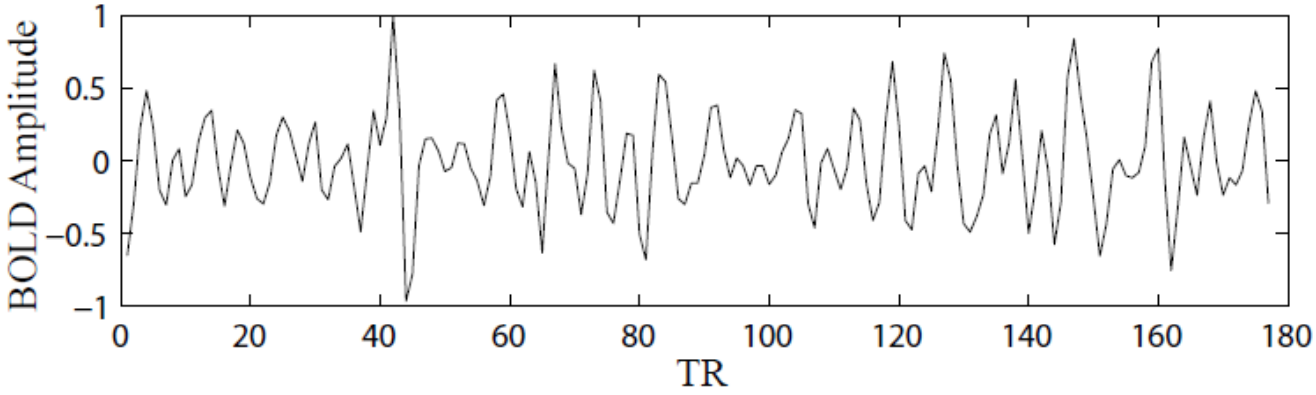
of resting state fMRI in schizophrenia

Diagnostics



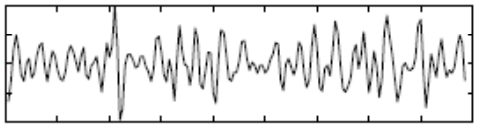
Univariate

(e.g., Entropy)

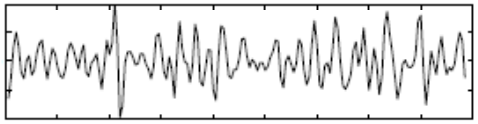


Multivariate

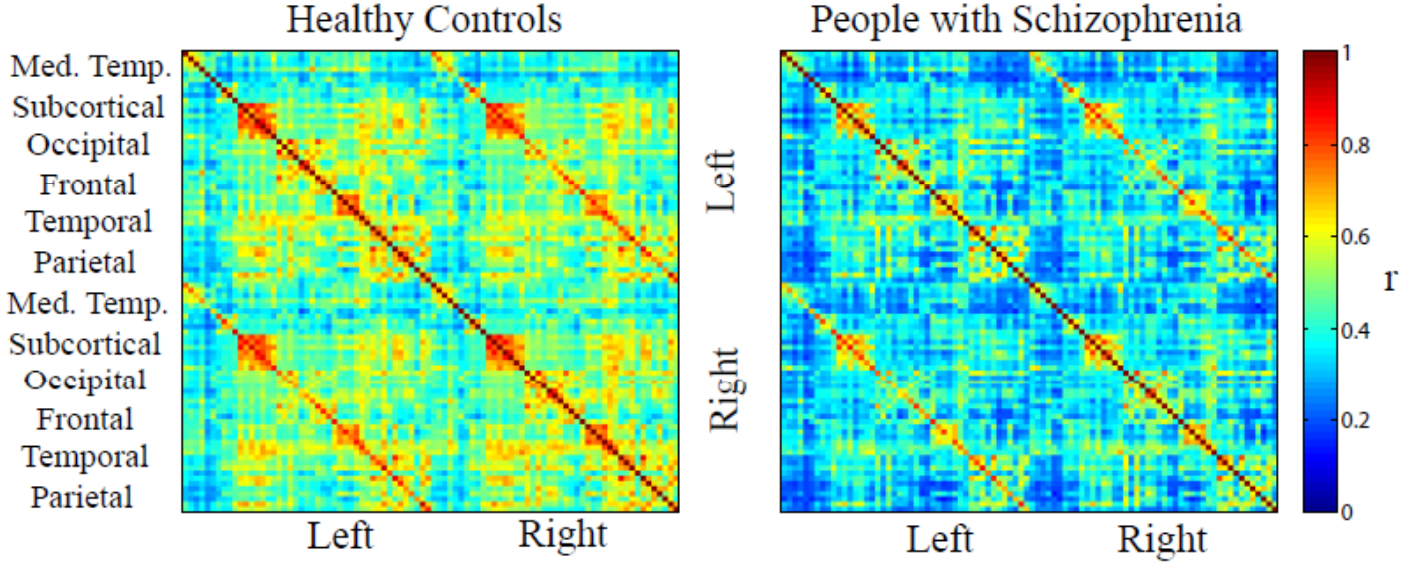
(e.g., Strength, Diversity)



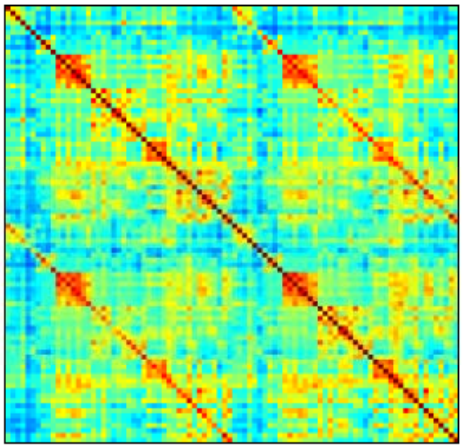
Bivariate correlation



Correlation Matrix

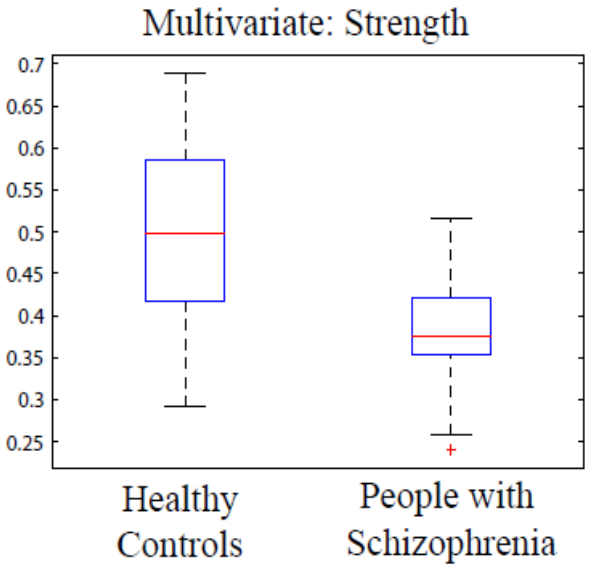


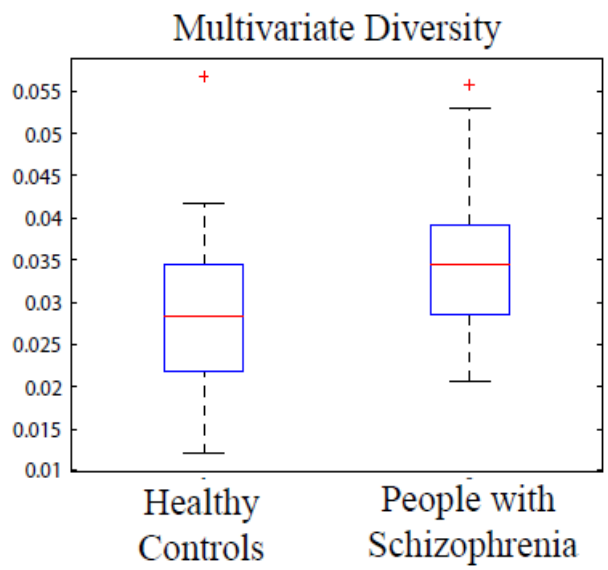
Group Differences in Multivariate Properties



Diversity: Average column variance

Strength: Average column mean



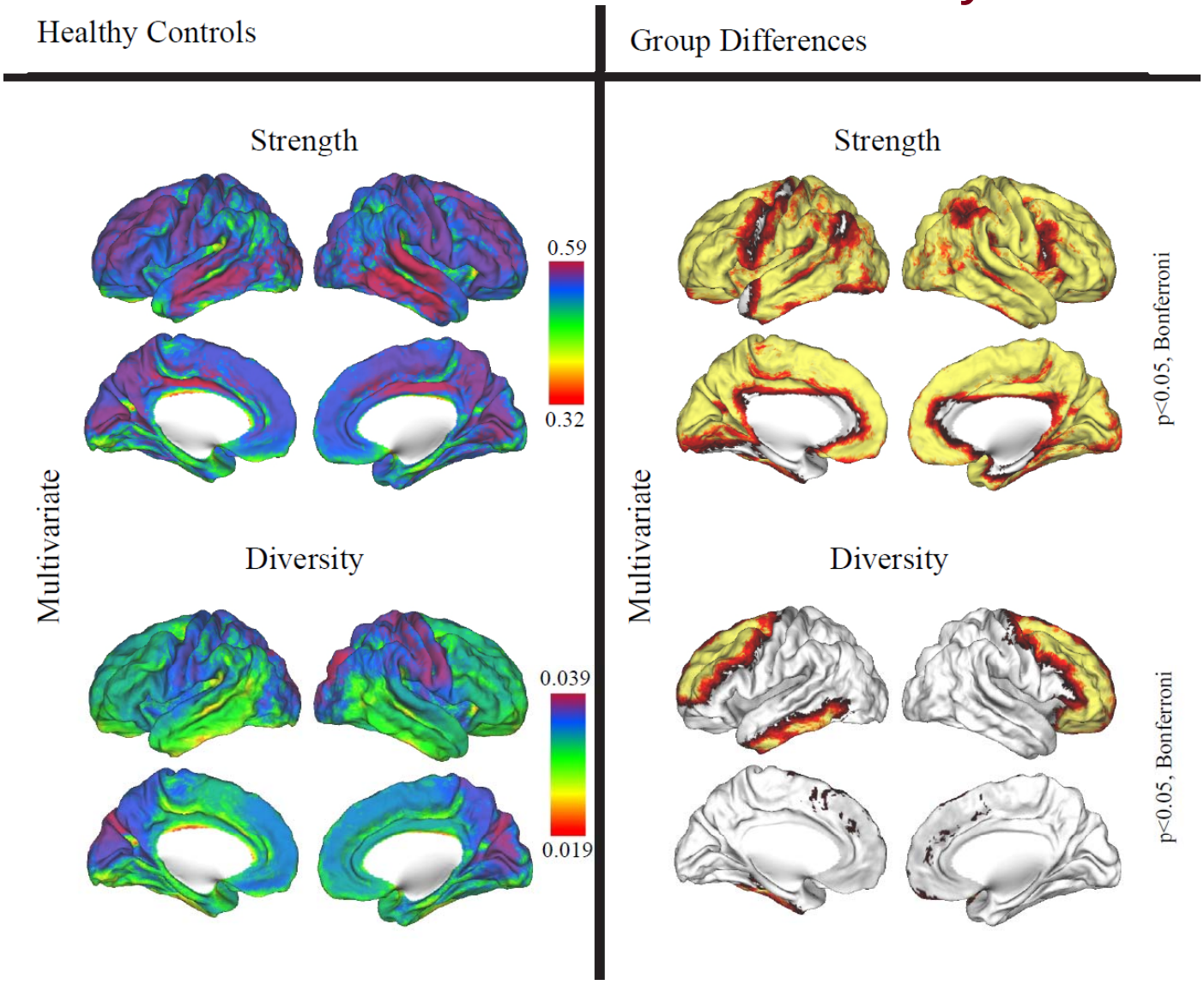


t = 4.86, p = 9.69e-6

t = 2.76, p = 0.0077

Group Differences in Regional Properties

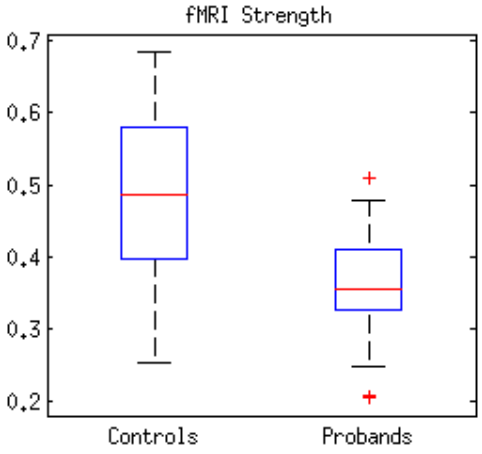
Multivariate Only



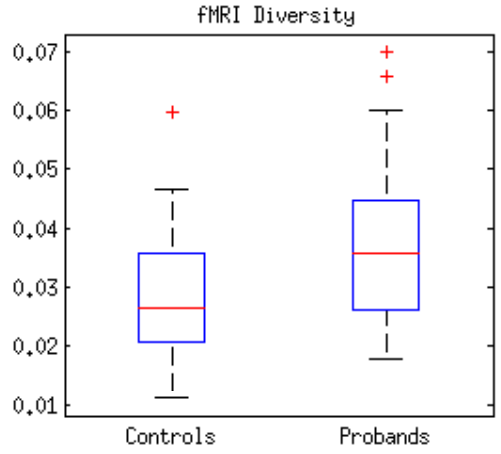
Regional group differences pass Bonferroni correction

(Since there are 90 brain regions, p<.05/90.)

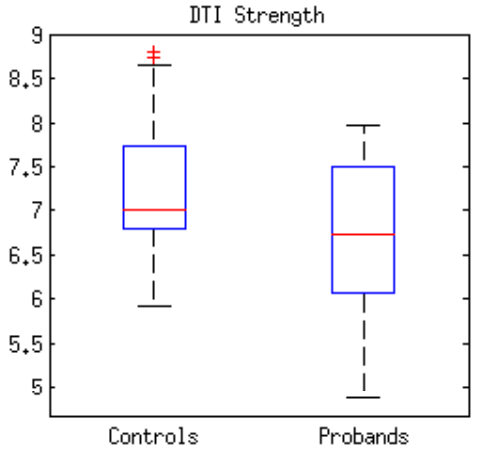
Group Differences fMRI and DTI



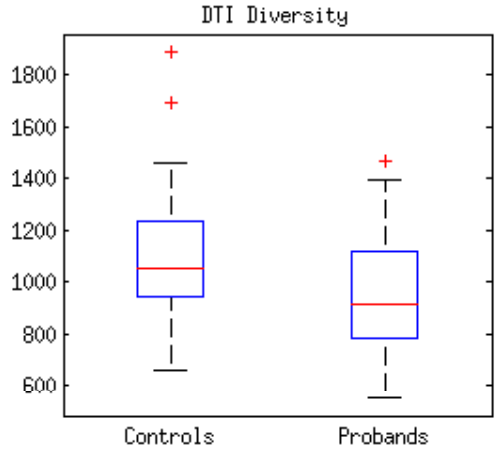
t = 4.86, p = 9.69e-6



t = 2.76, p = 0.0077



t =2.17, p =0.034

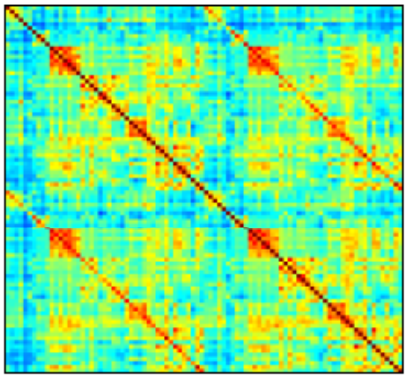


t = 2.43, p = 0.018

Multivariate rsfMRI Graph Complexity

Brain Graphs can be constructed by thresholding the correlation matrix

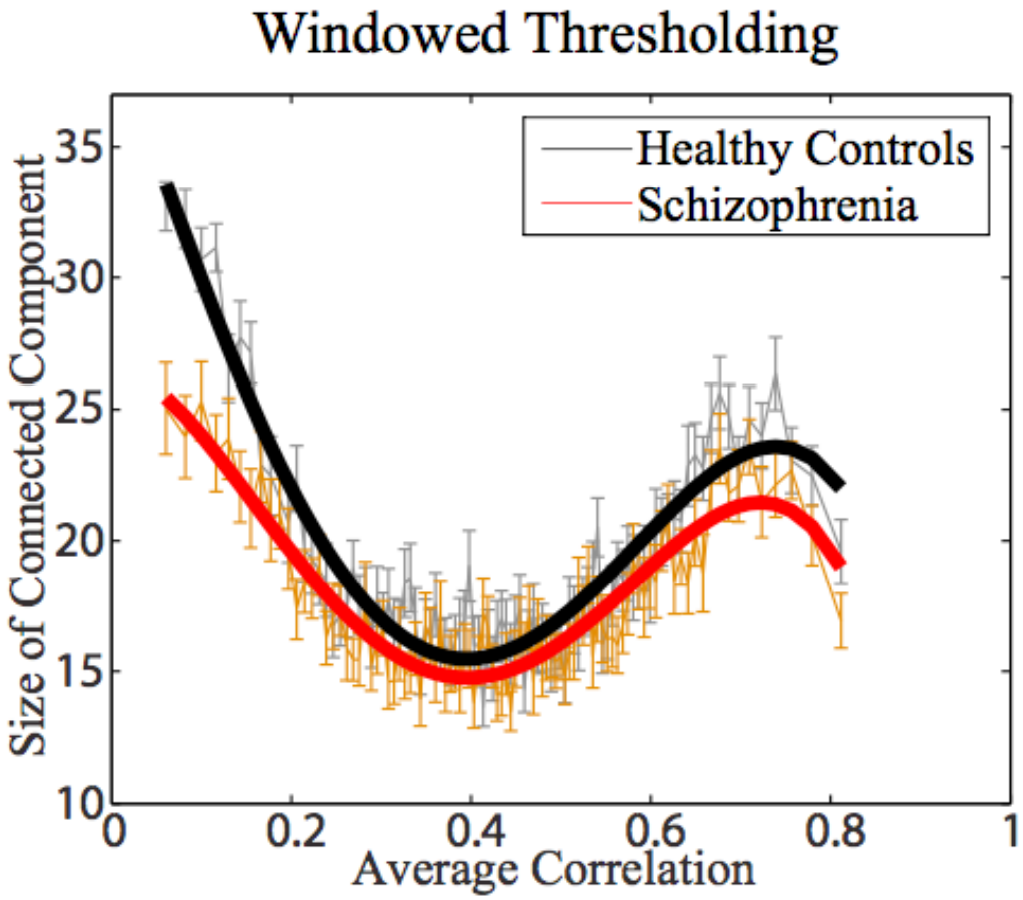
Correlation Matrix



Windowed thresholding allows us to examine the contributions of specific correlation ranges.

Group Differences in Graph Size

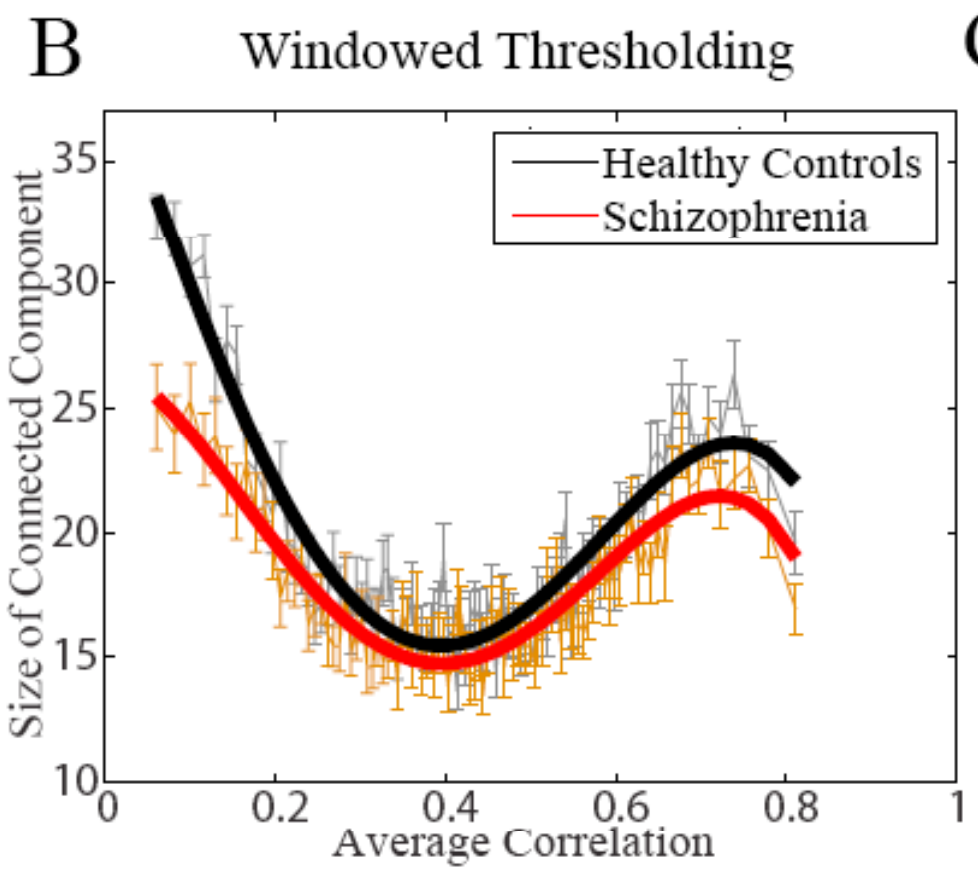
Group comparison of curves shows that the two curves have significantly different shapes ($p<5e-5$, using FDA).

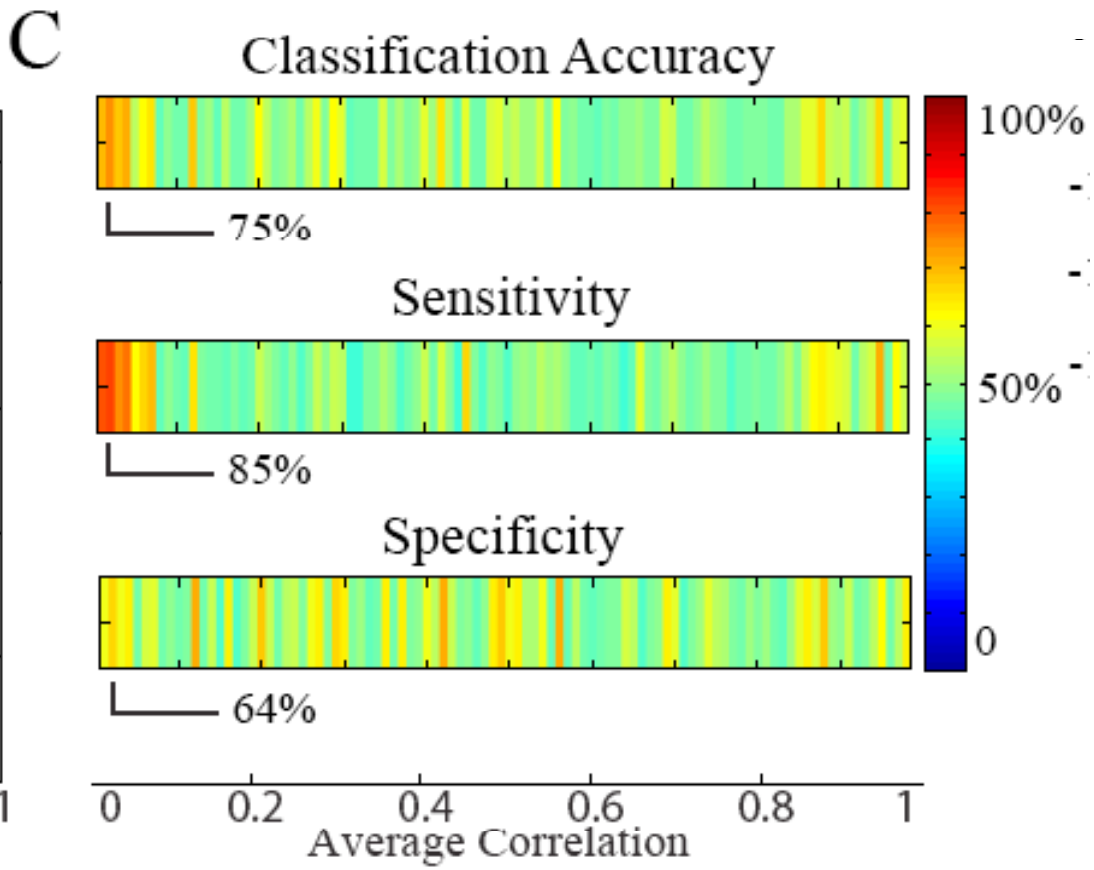


Curves diverge at the two endpoints.

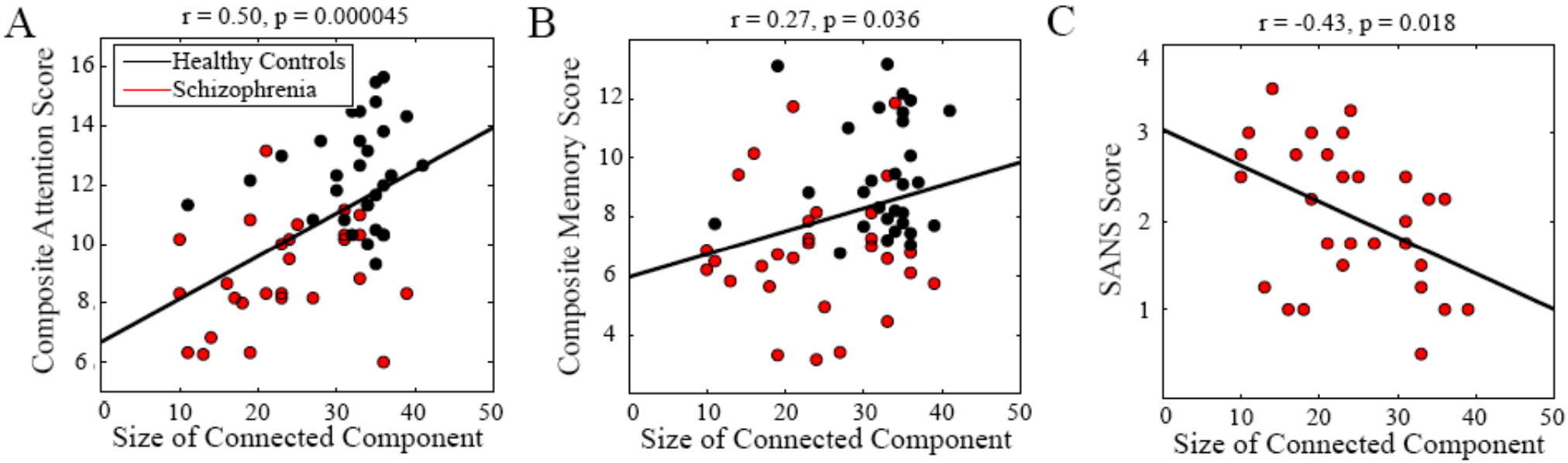
Weak and strong connections are the most discriminative between the groups.

Support Vector Machine





Clinical Correlates of Network Metrics



Moving from Nodes to Edges of Network

- Need to test every edge in network
- 90 nodes -> 4005 possible edges
- Type 1 Error control Bonferroni
  - p < .05 (5e-2) turns into p < 1.25e-5
- Loss of statistical power

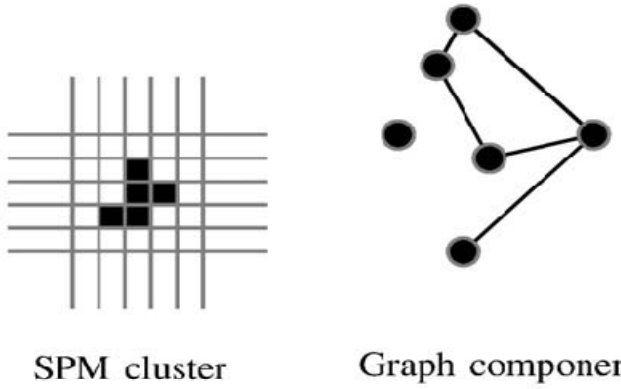
Statistical parametric map cluster

- Objective – identify voxels different between two groups
- Instead of examining single voxel, examine whether a cluster of voxels are different, based on a suprathreshold
- Permutation testing is performed with the data to determine the null distribution and the p value for the size of a cluster

Bullmore et al., IEEE Trans Med Imaging, 1999

Network Based Statistic (NBS)

- Apply the cluster size permutation strategy to the size of the network component

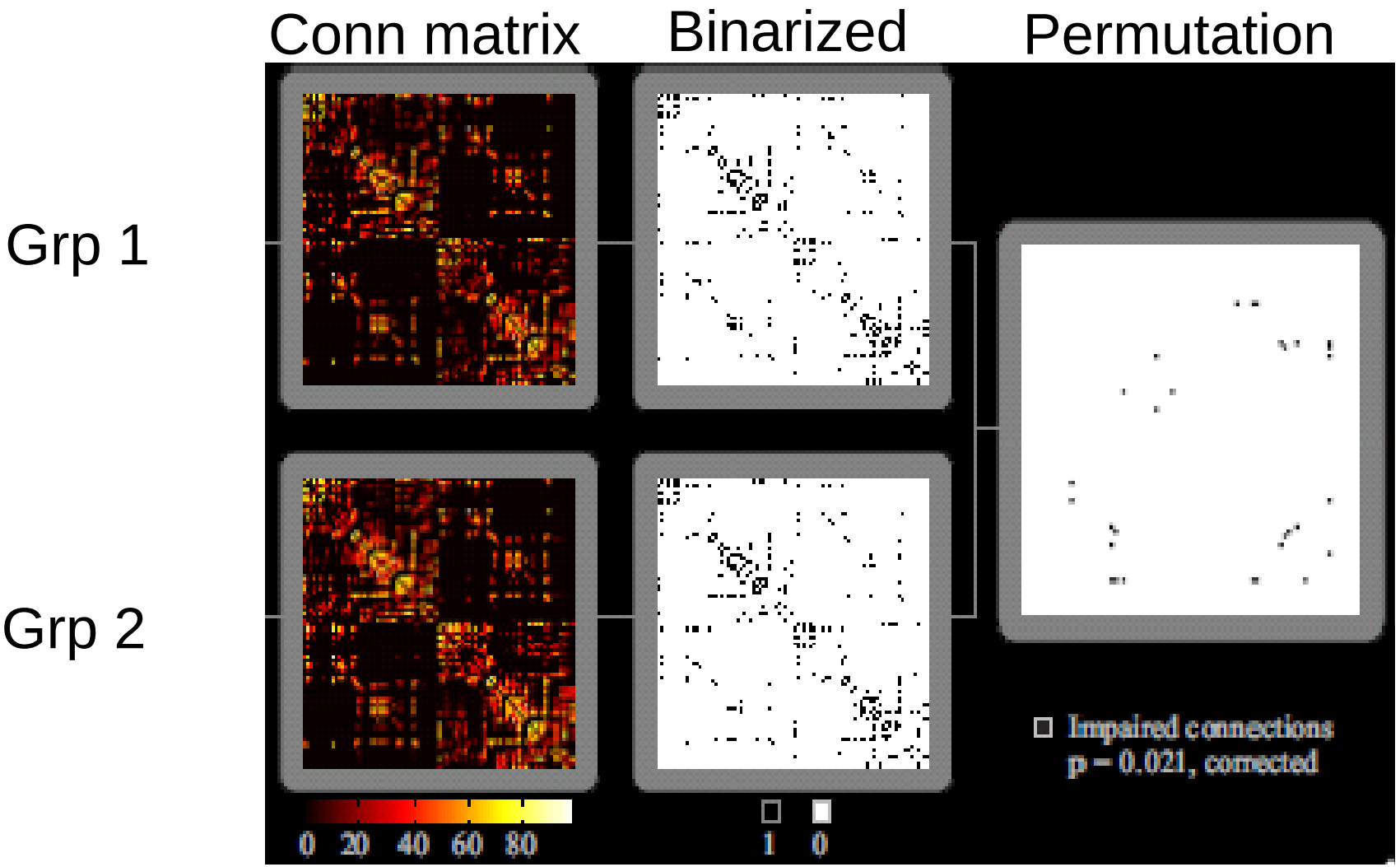


Zalesky et al., Neuroimage, 2010

Network Based Statistic - steps

- Objective – identify a graph component that is different between two groups
- Start with connectivity matrices
- Apply suprathreshold to all matrices
- Perform permutation analysis to determine null distribution of maximal size of graph component (number of edges)

NBS process



Zalesky et al., Biol Psychiatry, 2010

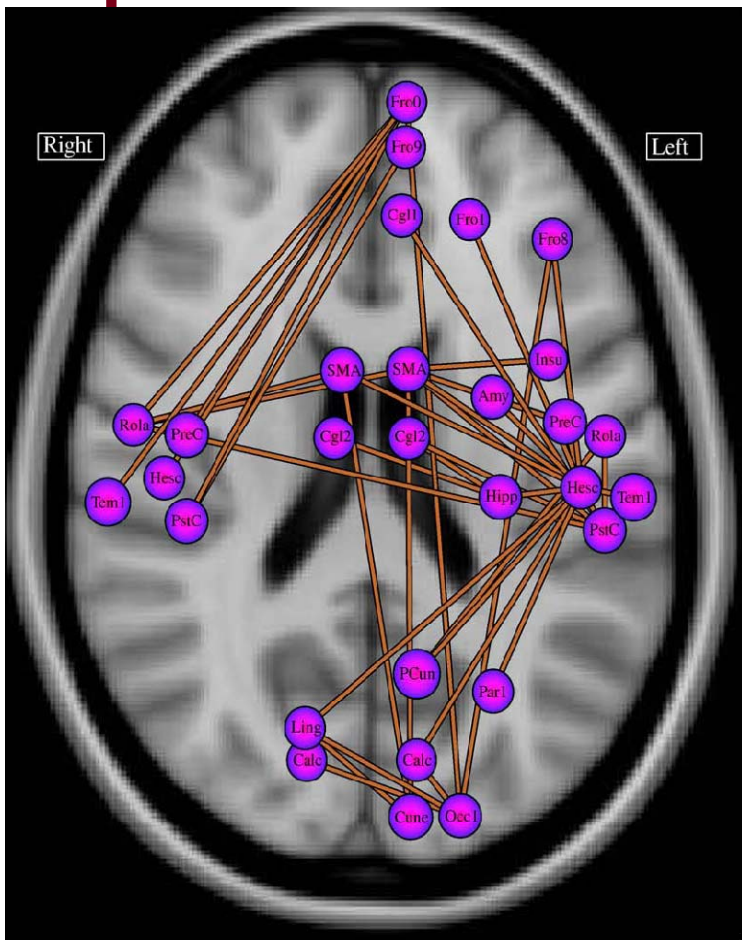
NBS – case control functional example

- rsfMRI collected on 12 patients with schizophrenia and 15 healthy volunteers
- 74 regions sampled, average time course obtained
- Wavelet transformed (.03<f<.06 Hz)
- 74x74 connectivity matrix created for each subject

Zalesky et al., Neuroimage, 2010

NBS – Dysconnected functional network in schizophrenia

- 29 nodes
- 40 edges (functional dysconnections)
- p = 0.037



Zalesky et al., Neuroimage, 2010

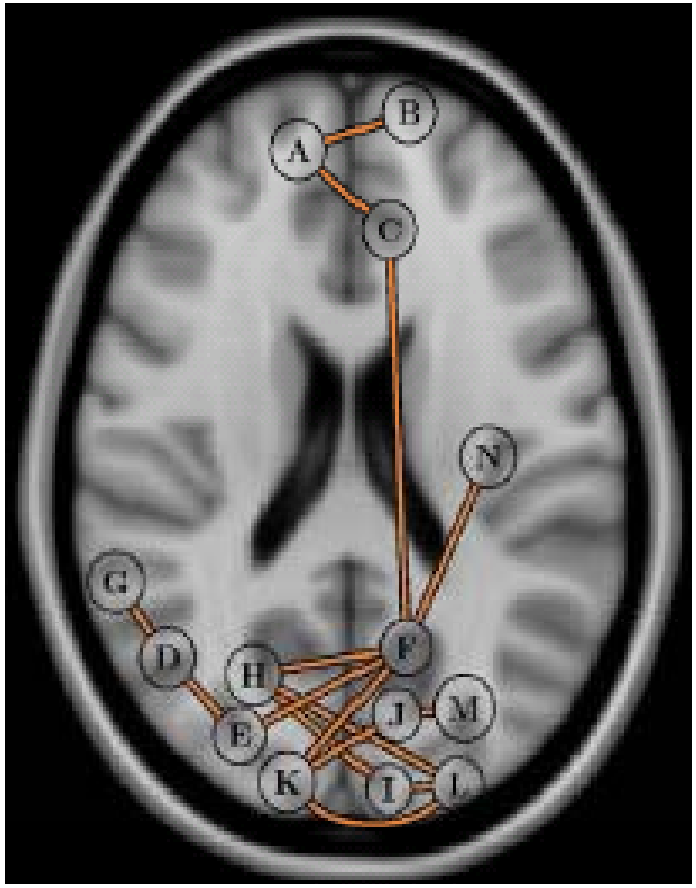
NBS – case control anatomical example

- DTI collected on 74 patients with schizophrenia and 32 healthy volunteers
- 82 regions – tractography used to determine number of streamlines between regions
- 82x82 connectivity matrix created for each subject

Zalesky et al., Biol Psychiatry, 2010

NBS – Disrupted anatomical network in schizophrenia

- 14 nodes
- 15 edges (anatomical dysconnections)
- $p < .021$



Zalesky et al., Biol Psychiatry, 2010

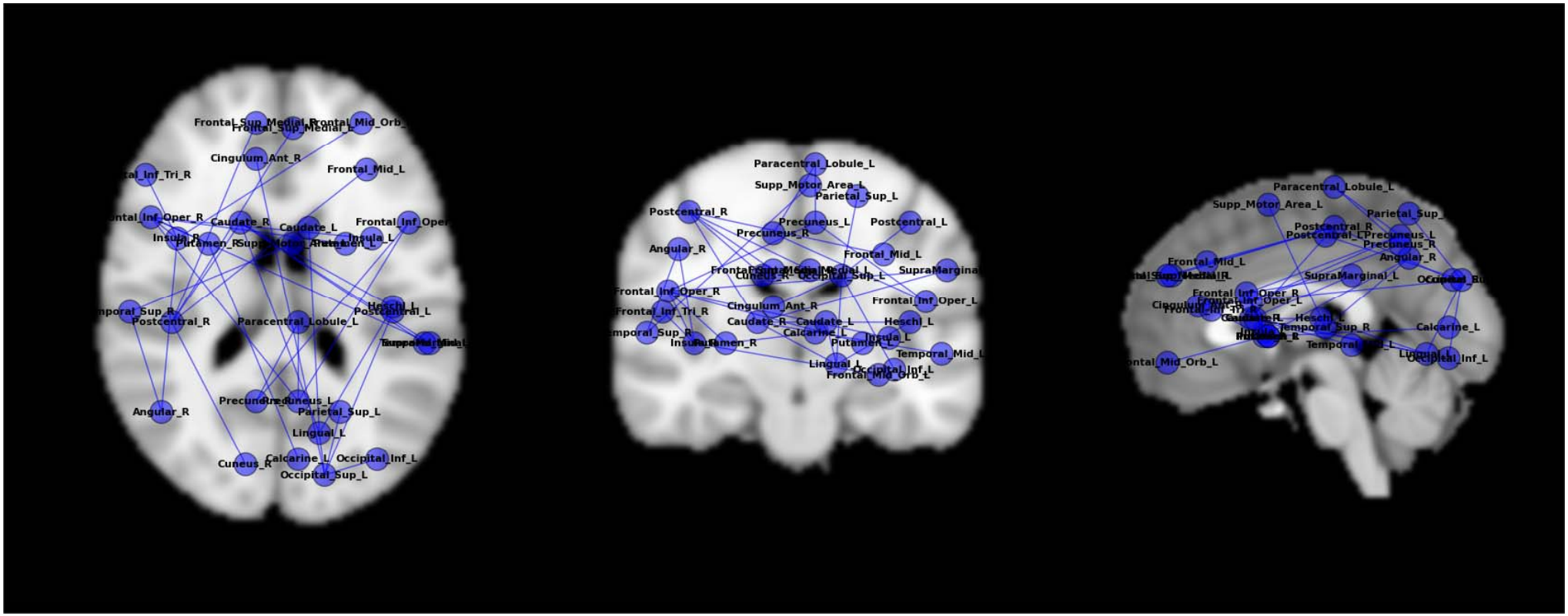
What is the overlap in anatomical and functional network abnormalities in schizophrenia?

- Need data from same subjects
- Have separate analyses of functional and anatomical connectivity
- How to combine?

Functional / Anatomical Common Node Analysis

- NBS analysis was done for fMRI and DTI
- A threshold was chosen for each modality so that the number of nodes and number of edges would be similar
- The nodal overlap between each modality was then computed

NBS – functional network



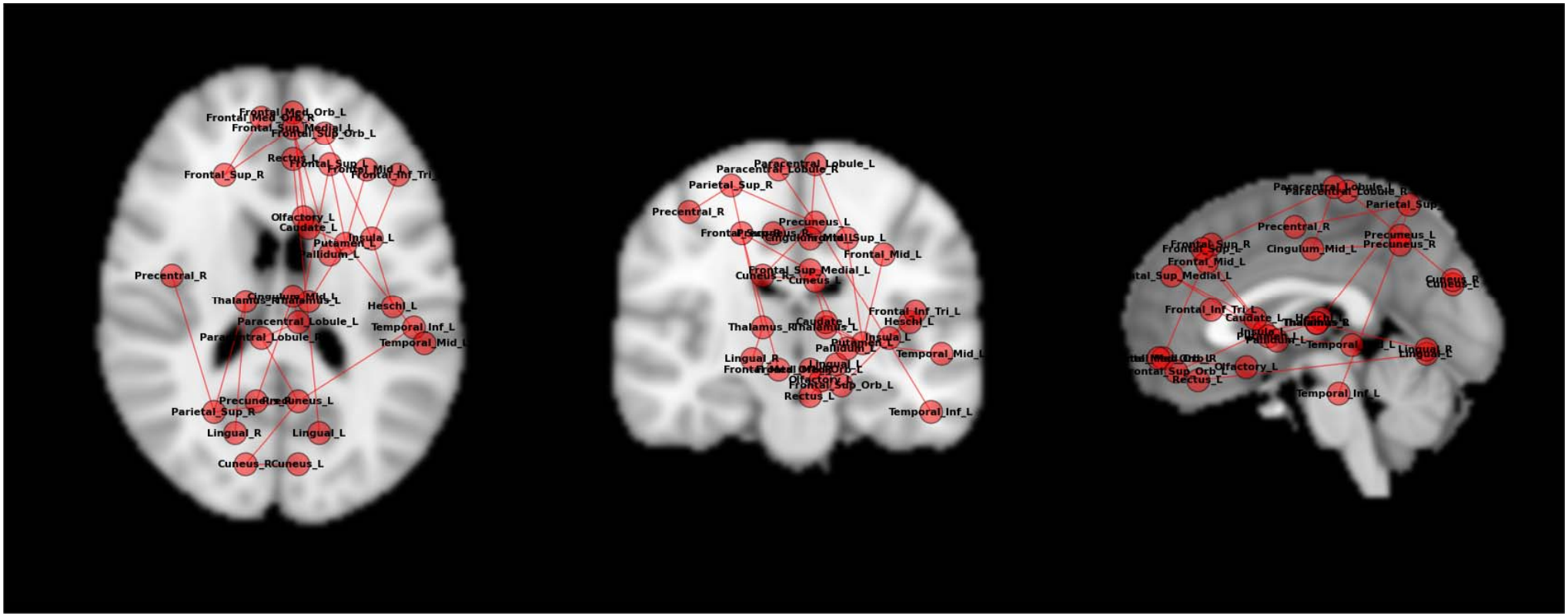
Nodes: 31 Edges: 32

Permutations: 500

T-stat: 3.2

P-Value: 0.009

NBS – anatomical network



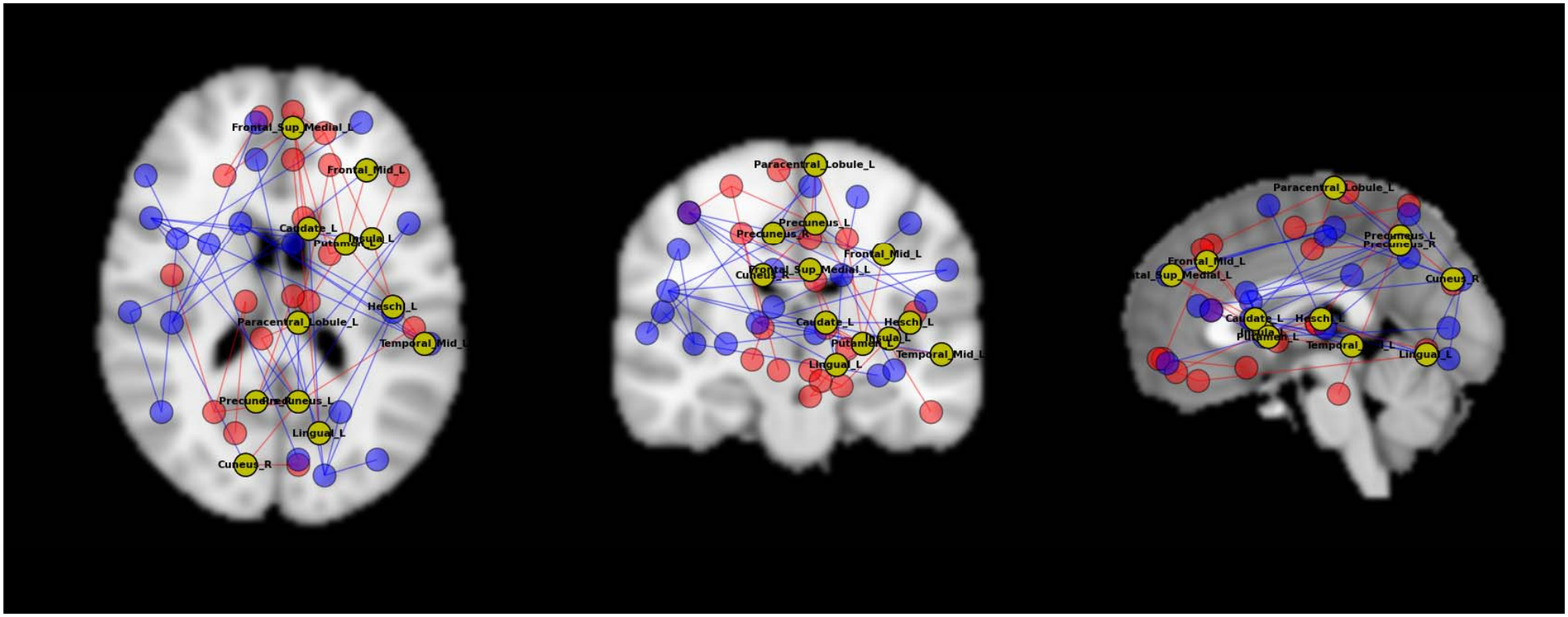
Nodes: 30 Edges: 30

Permutations: 500

T-stat: 2.15

P-Value: 0.003

Functional/Anatomical Network Node Overlap



- fMRI shown in blue
- DTI shown in red
- 12 overlapping nodes shown in yellow

Functional/Anatomical Network Node Overlap

- What is probability that 12 nodes would be found by chance?
- Performed a permutation analysis of combined functional and anatomical NBS analysis to determine null distribution of node overlap
- 10000 permutations, max node overlap was 10
- $P < 1xe-4$

Outline

- Multimodal Connectivity Imaging
  - DTI/DSI - Anatomical –wiring defect
  - Resting fMRI - Functional – signaling defect
- Network Analysis Approaches
  - Graph Theory
  - Multivariate
  - Graph metrics based on correlation strength
  - Network based statistics

Acknowledgements

- People
  - Bryon Mueller, Ph.D.
  - Chris Bell
  - Jazmin Camchong, Ph.D.
  - Angus MacDonald III, Ph.D.
  - Ryan Muetzel
  - Brent Nelson,M.D.
  - Angie Guimares
  - Paul Smiskol
  - Dani Bassett, Ph.D.
  - Steve Olson, M.D.
  - Elias Kersten

- Funding
  - R01MH060662
  - P20DA024196 – Center for the Study of Impulsivity in Addiction (CS*I*A)
  - MIND Institute
  - Office of Naval Research (DSB)
  - Wasie Foundation